IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicant(s): Kazuhiro FUKUNAGA et al
Serial No.: 10/509,839
Filed: April 1, 2003
For: viscous preparation for DENTAL USE CONTAINING BASIC FIBROBLAST GROWTH FACTOR
Art Unit: 1617
Examiner: Abigail M. Cotton

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

SIR:

I. Mr. Moriyuki Ohkuma, a citizen of Japan and having an address of 1-15-27-3, Takayanagi, Fujieda, Shizuoka, Japan, who declare and say as follows.

I finished from Faculty of Engineering, Department of Industrial Chemistry of Kogakuin University in 1979,

I was awarded the degree of Doctor of Pharmacy from Meijo University in 2000,

I have been employed by Kaken Pharmaceutical Co., Ltd. in April, 1974, and engaged in research and development on drug formulation as of today,

I am presently in charge of Drug Formulation Department at the Central Research Laboratories of the company; and

I understand the English language. I studied the Official Action dated March 13, 2006 received in the above-identified application.

In order to clarify that the present invention is not obvious over the references cited by the Examiner, I have conducted comparative experiments as mentioned below under my supervision.

II. Comparative experiments

In order to show excellent effect of using hydroxypropylcellulose as a thickener in combination with basic fibroblast growth factor (bFGF), the following experiments are carried out.

1. Experimental materials

In the experiment, the following materials were used.

bFGF (Trafermin (genetical recombination)) (available from Scios Inc., U.S.A.)

Hydroxypropylcellulose (available from Nippon Soda Co., Ltd., Japan)

Fibrinogen (available from ITO LIFE SCIENCES INC., Japan) used in Asano et al.

Sodium carboxymethylcellulose (available from Dai-ichi Kogyo Seiyaku Co., Ltd., Japan) mentioned in Finkenaur

Hydroxypropylmethylcellulose (available from Shin-Etsu Chemical Co., Ltd.) mentioned in Finkenaur

Methylcellulose (available from Shin-Etsu Chemical Co., Ltd.) mentioned in Finkenaur

2. Experimental method

An aqueous solution containing a predetermined concentration of bFGF and a predetermined concentration of a

thickener was prepared, allowed to stand at 25°C for 24 hours, a purity of bFGF remained in the aqueous solution was measured. Also, for a control, no thickener was formulated.

3. Analysis method

By using 250 μL of the respective sample solutions after allowing to stand at 25°C for 24 hours, a purity of bFGF was measured by reverse phase HPLC (High performance liquid chromatography).

4. Evaluation standard

A purity of bFGF at the time of starting the experiment of the control solution was made 100%, and a remaining ratio of the bFGF in the respective sample solutions was compared with the initial amount. A sample in which an amount of the bFGF is substantially not changed as compared with the initiation of the experiment is judged to have good stability.

5. Results

The results are as shown in the following Table.

	bFGF concentration	Thickener concentration	bFGF remaining ratio (%)		Preparation
			At the time of initiation	24 hours later	
Hydroxypropyl cellulose	4 mg/L	3%	99.5	98.2	○
Fibrinogen	4 mg/L	4.16%	--[3]		×
Sodium carboxymethyl cellulose	4 mg/L	3%	--[2]		×
Hydroxypropyl methylcellulose	4 mg/L	3%	98.7	93.2	×

Methylcellulose	4 mg/L	3%	98.0	90.4	×

1) Fibrinogen is modified or denatured so that stability of bFGF could not be confirmed.

2) Turbid was observed, which is derived from bFGF, so that measurement was not carried out.

6. Consideration

As can be seen from the results shown in the above Table, it can be understood that hydroxypropylcellulose used in the present invention showed good stability as a viscous preparation.

On the other hand, when bFGF is used in combination of fibrinogen as mentioned in Asano et al., stability of bFGF could be measured. Also, when other cellulose derivatives than the present invention are used, such as hydroxypropylmethylcellulose which is mentioned as a preferred one in Finkenaur, the bFGF concentration was reduced more than 5% and cannot be used as a viscous preparation of the present invention.

III. Conclusion

I believe that the above results would indeed be surprising and could never be expected from the description of the cited references. Thus, I do not believe that the present invention is obvious over the references cited by the Examiner.

IV. I further declare that all statements made herein of may own knowledge are true and that all statements made in information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable

by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: June 20, 2006

Moriyuki Ohkuma

Moriyuki Ohkuma